REMARKS

By the present communication new claims 52-54 are added. Claims 1-28 were previously canceled without prejudice to pursuing the subject matter of these claims in one or more applications claiming priority to the above-captioned application. Following entry of the amendments claims 29-54 will be under examination.

Support for the new claims 52-54 can be found in the specification, for example, at page 51, lines 9-29 and page 52, lines 8-34. The description of Figure 1 has been amended to correct an obvious error. Accordingly, the amendments do not raise any issues of new matter. Therefore, entry of the amendments is respectfully requested.

Information Disclosure Statement

Applicants request consideration of the references cited in the Information Disclosure Statement submitted herewith. The references were cited by the United States Patent and Trademark Office during prosecution of copending applications US Ser. No. 10/767,476 and US Ser. No. 09/606,369 which are priority related to the instant application.

Rejections Under 35 U.S.C. § 102

Claims 29, 30, 33, 38, 39, 41-44, 48 and 49 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Landegren (US 5,618,701).

Applicants respectfully traverse the rejection. The claims require, *inter alia*, "providing a second substrate comprising a plurality of array locations, each array location comprising a plurality of discrete sites, wherein said sites comprise different bioactive agents." The Office appears to hold that the multipronged solid support (described at column 2, lines 11-12) or manifolds having plurality of individual solid-phase members (described at column 2, lines 31-37) of Landegren are the same as the second substrate recited in the claims. However, the Office has not pointed to any description in Landegren of an individual prong or member that has an array location having a plurality of different bioactive agents. Applicants also can find no such

description in Landegren. Rather, Landegren describes a method in which the sequence is determined for a *single species* of nucleic acid attached at each prong or individual member of the substrate. The sequencing method of Landegren is carried out such that a single species of nucleic acid attached to each tooth of the comb-like substrate is subjected to a sequencing reaction, reaction products from each tooth are eluted into a discrete well of a gel and the reaction products in that well are separated by electrophoresis such that the sequence of the nucleic acid can be determined from the pattern of bands on the gel (see, for example, column 5, line 25, through column 6, line 34 of Landegren). Accordingly, each tooth contains only a single species of nucleic acid. Moreover, the presence of multiple different species of nucleic acid on a single tooth would produce a mixture of sequencing reaction products that could not be resolved one from the other in a single lane of a gel using the methods of Landegren. Absent a description of all elements of the claims, the cited reference is not anticipatory. Accordingly, reconsideration and withdrawl of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 31-32, 34-37, 40, and 45-47 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Landegren (US 5,618,701) in view of Fodor et al. (US 5,800,922). In making the rejection, the Office Action relies upon the characterization of Landegren set forth in the novelty rejection. The Office Action points out that Landegren does not describe several of the elements recited in claims 31-32, 34-37, 40, and 45-47. The Office Action alleges that Fodor et al. describes the missing elements.

Applicants respectfully traverse the rejection. The claims require, *inter alia*, "providing a second substrate comprising a plurality of array locations, each array location comprising a plurality of discrete sites, wherein said sites comprise different bioactive agents." Because claims 31-32, 34-37, 40, and 45-47 depend from claim 29, they all require this step. Applicants' remarks below are made specifically with respect to elements recited in claim 29, but pertain to all dependent claims.

Applicants maintain for the reasons set forth above in response to the novelty rejection that Landegren does not teach or suggest all of the elements of base claim 29, including, for example, "providing a second substrate comprising a plurality of array locations, each array location comprising a plurality of discrete sites, wherein said sites comprise different bioactive agents." As the rejection stands, the Office has failed to articulate a *prima facie* case of obviousness because a motivation, teaching or suggestion to combine the cited references to arrive at the claimed method has not been provided.

In making the rejection, the Office Action alleges that column 20, lines 13-37 of Fodor et al. "discloses a method of generating the desired repertoire of oligonucleotide probes on a substrate wherein the densities could range from 5 regions/cm^2 to an excess of one million regions/cm^2." See page 6, lines 5-7 of the Office Action mailed November 1, 2006. The Office Action goes on to assert that "it would have been obvious to apply the varying densities of bioactive agents at array locations by Fodor et al. to the method of dipping an array containing a plurality of bioactive agents, into a second substrate of target analytes as taught by Landegren." See page 6, lines 8-11 of the Office Action mailed November 1, 2006. However, the Office Action fails to articulate any motivation whatsoever for making such a modification to the methods of Landegren.

The "mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole." *In re Kahn*, Case No. 04-1616, slip op. at 11 (Fed. Cir. March 22, 2006) (citing *In re Rouffet*, 149 F.3d 1350, 1355, 1357 (Fed. Cir. 1998)). To establish a *prima facie* case of obviousness based upon a combination of elements across different references, the law requires that "at the time the invention was made" (35 U.S.C. § 103; *In re Kahn*, Case No. 04-1616, slip op. at 12) "there be a suggestion, motivation or teaching to those skilled in the art for such a combination." *Iron Grip Barbell, Co. v. York Barbell, Co.*, Case No. 04-1149, slip op. at 5 (Fed. Cir. December 14, 2004) (citing *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988)). This requirement prevents the use of "the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight." *Id.*; *see also In re Kahn*, Case No. 04-1616, slip op. at 12.

Applicants submit that there would not have been any motivation to make the alleged combination because the two references describe methods that are *alternative* means to achieve the same result. As set forth above in response to the novelty rejection, Landegren uses prongs to separate each target nucleic acid such that individual prongs can be contacted with separate reagent wells and then each prong can be contacted with a separate well of a gel for electrophoresis, whereby the sequence of the target nucleic acid in each lane of the gel can be individually determined. On the other hand, Fodor et al. separate individual target nucleic acids via spatial separation at known locations on a substrate such that the substrate surface can be treated with reagents in a batch fashion and each target can be individually detected using a high resolution scanner. Each method is an alternative means to separate target sequences into an "array" for parallel analysis of the individual target sequences. There is no teaching or suggestion of a second level of separation in which two more of these arrays are separated from each other.

In contrast, the claimed methods use an "array of arrays" in which, not only are different bioactive agents separated from each other on an array, but multiple arrays are also present on the same substrate and separated from each other. As taught on the specification

> The invention relates to sensor compositions comprising a composite array of individual arrays, to allow for simultaneous processing of a number of samples.

Page 1, lines 10-11, and

> The present invention is directed to the formation of very high density arrays that can allow simultaneous analysis, i.e. parallel rather than serial processing, on a number of samples. This is done by forming an "array of arrays", i.e. a composite array comprising a plurality of individual arrays, that is configured to allow processing of multiple samples.

Page 5, line 36, through page 6, line 2. Applicants' specification teaches that an advantage of using a substrate having a plurality of array locations is the ability to do parallel analysis rather than sequential analysis of arrays. The art does not identify the need or any benefit to processing several arrays in parallel and it is only with the benefit of hindsight using Applicants' specification that any reasoning can be found to combine the cited references to arrive at Applicants claimed invention.

Furthermore, modification of the Landegren methods as suggested by the Office Action would render the methods unsuitable for their intended use. In this regard the Office Action appears to suggest modifying the Landegren methods such that each tooth of the comb-like substrate would include an array of different bioactive agents attached. However, the sequencing method of Landegren is carried out such that a single species of nucleic acid attached to each tooth of the comb-like substrate is subjected to a sequencing reaction and reaction products from each tooth are eluted into a discrete well of a gel and the reaction products in that well are separated by electrophoresis such that the sequence of the nucleic acid can be determined from the pattern of bands on the gel (see, for example, column 5, line 25, through column 6, line 34 of Landegren). The presence of multiple different species of nucleic acid on a single tooth, which would necessarily result from the combination alleged in the Office Action, would produce a mixture of sequencing reaction products that could not be resolved one from the other in a single lane of a gel using the methods of Landegren. If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); as cited in MPEP 2143.01(V). Therefore, the subject matter of the claims would not have been obvious over Landegren in view of Fodor et al. Reconsideration and withdrawl of the rejection is respectfully requested.

Claims 29-47 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Ishikawa et al. (US 5,888,834) in view of Fodor et al. (US 5,800,922).

Applicants respectfully traverse the rejection. In making the rejection, the Office Action alleges that Ishikawa et al., describe use of a dipstick coated with a receptor that is inserted into the well of a solid phase. The Office acknowledges that Ishikawa et al. do not discuss a method wherein the dipstick type solid phase comprises a plurality of different array locations nor do they discuss the wells containing sample solutions of a plurality of different bioactive agents. The Office alleges that Fodor et al. provides the missing elements. However, as the rejection stands, the Office has failed to articulate a *prima facie* case of obviousness because a motivation,

teaching or suggestion to combine the cited references to arrive at the claimed method has not been provided. The Office merely alleges that

> [i]t would have been obvious to one of ordinary skill in the art at the time of the invention to add a substrate comprising a plurality of array locations, comprising a plurality of different bioactive agents for detecting a plurality of target analytes, wherein the method is used to detect mismatched bases (i.e. single nucleotide polymorphisms) within a fluorescently labeled target, or to detect polymers carbohydrates, or polypeptides as taught by Fodor et al. to the method of dipping an array coated with a bioactive agent into a second substrate comprising a target analyte as taught by Ishikawa et al. The skilled artisan would have had a reasonable expectation of success in adding a plurality of array locations bioactive agents, and target analytes, and further add the detection of SNPs in target nucleic acids, or the detection of polymers, carbohydrates, or polypeptides to the method of Ishikawa et al.

See page 10, lines 1-11 of the Office Action mailed November 1, 2006. The above statements are conclusory amounting to no more than an allegation that it would have been obvious to combine the references and that there would have been a reasonable expectation of success in combining the references. There is no motivation provided here or anywhere in the Office Action to support a *prima facie* case of obviousness.

The "mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole." *In re Kahn*, Case No. 04-1616, slip op. at 11 (Fed. Cir. March 22, 2006) (citing *In re Rouffet*, 149 F.3d 1350, 1355, 1357 (Fed. Cir. 1998)). To establish a *prima facie* case of obviousness based upon a combination of elements across different references, the law requires that "at the time the invention was made" (35 U.S.C. § 103; *In re Kahn*, Case No. 04-1616, slip op. at 12) "there be a suggestion, motivation or teaching to those skilled in the art for such a combination." *Iron Grip Barbell, Co. v. York Barbell, Co.*, Case No. 04-1149, slip op. at 5 (Fed. Cir. December 14, 2004) (citing *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988)). This requirement prevents the use of "the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight." *Id.*; *see also In re Kahn*, Case No. 04-1616, slip op. at 12.

Applicants submit that there would not have been any motivation to make the alleged combination because as is the case for the alleged combination with Landegren and Fodor et al., the Ishikawa et al. and Fodor et al. references describe methods that are *alternative* means to achieve the same result. As set forth above, Fodor et al. separate individual target nucleic acids via spatial separation at known locations on a substrate such that the substrate surface can be treated with reagents in a batch fashion and each target can be individually detected using a high resolution scanner. On the other hand, Ishikawa et al. uses dipsticks to separate individual receptors for contact with fluorescently labeled samples and discrete detection of binding. Each method is an alternative means to separate target sequences into an "array" for parallel analysis of the individual target sequences. There is no teaching or suggestion of a second level of separation in which two more of these arrays are separated from each other.

In contrast, the claimed methods use an "array of arrays" in which, not only are different bioactive agents separated from each other on an array, but multiple arrays are also present on the same substrate and separated from each other, as taught in the specification. Applicants' specification teaches that an advantage of using a substrate having a plurality of array locations is the ability to do parallel analysis rather than sequential analysis of arrays (see, for example, page 5, line 36, through page 6, line 2 of the specification which is quoted above). The art does not identify the need or any benefit to processing several arrays in parallel and it is only with the benefit of hindsight using Applicants' specification that any reasoning can be found to combine the cited references to arrive at Applicants claimed invention. Absent any motivation to combine the cited references the claims would not have been obvious. Reconsideration and withdrawl of the rejection is respectfully requested.

Claims 34-37 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Landegren (US 5,618,701) in view of Burbaum et al. (US 5,876,946).

Applicants respectfully traverse the rejection. The claims require, *inter alia*, "providing a second substrate comprising a plurality of array locations, each array location comprising a plurality of discrete sites, wherein said sites comprise different bioactive agents." Because claims 34-37 depend from claim 29, they all require this step. Applicants' remarks below are

made specifically with respect to elements recited in claim 29, but pertain to all dependent claims.

As set forth above in response to the novelty rejection, Landegren does not teach or suggest all of the elements of base claim 29, including, for example, "providing a second substrate comprising a plurality of array locations, each array location comprising a plurality of discrete sites, wherein said sites comprise different bioactive agents." Burbaum et al. does not cure the deficiencies of Landegren because Burbaum et al. does not describe a second substrate comprising a plurality of array locations, each array location comprising a plurality of discrete sites, wherein said sites comprise different bioactive agents. At best Burbaum et al. describes a collection of suspendable solid supports, such as a beads, that each have a single species of target molecule attached. See column 6, lines 18-21 and column 8, lines 26-44. There is no description in Burbaum et al. of the suspendable solid supports, or any solid support, having a plurality of discrete sites comprising different bioactive agents. Furthermore, the collection of particles does not constitute a substrate that is dipped into assay wells as claimed because the particles in the collection are physically separate from each other. Therefore, Landegren and Burbaum et al. taken alone or in combination do not teach or suggest all of the claimed elements and the claims are not obvious. Reconsideration and withdrawl of the rejection is requested.

Claims 29, 34-39, 40-45 and 48-51 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Ishikawa et al. (US 5,888,834) in view of Burbaum et al. (US 5,876,946).

Applicants respectfully traverse the rejection. In making the rejection, the Office Action alleges that Ishikawa et al., describe use of a dipstick coated with a receptor that is inserted into the well of a solid phase. The Office Action acknowledges that Ishikawa et al. do not discuss a method wherein the dipstick type solid phase comprises a plurality of different array locations nor do they discuss the wells containing sample solutions of a plurality of different bioactive agents. The Office alleges that Bubaum et al. provides the missing elements. However, as the rejection stands, the Office has failed to articulate a *prima facie* case of obviousness because a motivation, teaching or suggestion to combine the cited references to arrive at the claimed method has not been provided. Rather the statements made by the Office action are conclusory

amounting to no more than an allegation that it would have been obvious to combine the references and that there would have been a reasonable expectation of success in combining the references (see page 17, line 13, through page 18, line 2 of the Office Action mailed November 1, 2006). There is no motivation provided here or anywhere in the Office Action to support a *prima facie* case of obviousness.

Furthermore, Burbaum et al. does not cure the deficiencies of Ishikawa et al. because Burbaum et al. does not describe "a second substrate comprising a plurality of array locations, each array location comprising a plurality of discrete sites, wherein said sites comprise different bioactive agents" as claimed. At best Burbaum et al. describes a collection of suspendable solid supports, such as a beads, that each have a single species of target molecule attached. See column 6, lines 18-21 and column 8, lines 26-44. There is no description in Burbaum et al. of the suspendable solid supports, or any solid support, having a plurality of discrete sites comprising different bioactive agents. Furthermore, the collection of particles does not constitute a substrate that is dipped into assay wells as claimed because the particles in the collection are physically separate from each other. Therefore, Ishikawa et al. and Burbaum et al. taken alone or in combination do not teach or suggest all of the claimed elements and the claims are not obvious. Reconsideration and withdrawl of the rejection is respectfully requested.

CONCLUSION

In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent should there be any questions.

Respectfully submitted,

Date: March 12, 2007

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